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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,570	09/27/2004	Julio Cesar Aguilar Rubido	976-18 PCT/US	9315

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EXAMINER	
PENG, BO	
ART UNIT	**PAPER NUMBER**
1648	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,570	RUBIDO ET AL.	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/2/07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *4-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 13-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/6/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 2, 2007, has been entered.

2. This Office Action is in response to the amendment filed March 2, 2007. Claims 1-20 are pending. Claims 1, 14 and 15 are amended. Claims 4-12 were withdrawn as non-elected. Claims 1-3 and 13-20 are under consideration in this Office action. Claim 13 reads on Applicant's elected species, wherein the multivalent vaccine formulation comprising HBV surface antigen (HBsAg) with tetanus toxoid antigen (TT), diphtheria toxoid antigen (DT), *Bordetella pertussis* (Bp), and anti-*Haemophilus influenzae* type b (Hib),

Information Disclosure Statement

3. Applicant's IDS form 1449 submitted on March 6, 2007 has been considered by the examiner. The initialed and dated copies of IDS form 1449 are attached to the instant Office action.

35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The rejection of Claims 1-3 and 13-20 under 35 U.S.C. 103(a), as being obvious over Schmitt (2000), Alpar (2001) and Isaka (2001), **is withdrawn** in view of the amendment.

6. Following is a new ground of rejection necessitated by Applicant's amendment.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-3 and 13-20 are rejected under 35 U.S.C. 103(a) as being obviousness over Schmitt (2000), Alpar (2001) and Isaka (2001), all in view of EP 0864649A2 (1998).

9. Claims 1-3 and 13-20 are directed to a multivalent vaccine formulation for nasal administration comprising HBsAg produced by *Pichia pastoris* and a number of 1 to 5 other antigens, wherein the HBsAg is a mucosal immunoenhancer of soluble antigens, *Bordetella pertussis* and inactivated poliovirus, wherein the other antigens are tetanus toxoid antigen (TT),

diphtheria toxoid antigen (DT), a conjugate protein-polysaccharide corresponding to a vaccine antigen anti-*Haemophilus influenzae* type b (Hib), a conjugate protein-polysaccharide corresponding to polysaccharide C of *Neisseria meningitides* conjugated to a carrier protein, a conjugate protein-polysaccharide wherein the polysaccharide part corresponds to a vaccine polysaccharide of *Pneumococcus pneumoniae*, inactivated microorganisms, the bacterin *Bordetella pertussis*(Bp), inactivated virus, attenuated virus, or mixtures of them and other antigenic types, which receive an immunoenhancing effect because of their co-administration with HBsAg, wherein the antigens are TT, DT, Hib and Bp, wherein the volume of the final formulation is ranging from 50 microliters to 2 milliliters, wherein the amount of antigen to be inoculated range from 0.1 micrograms to 2 mg, wherein the antigen mixture is dissolved in PBS, saline solution, water for injection or in any buffer solution used in medical practice or that allows the stability of the antigens.

10. Schmitt teaches multivalent vaccine formulations comprising HBsAg + DTaP+Hib + inactivated poliovirus given as either separate or mixed injection. The multivalent vaccines have been tested in a total of 359 infants of 2, 3 and 4 months of age. Schmitt teaches that the multivalent formulations are safe, immunogenic and well tolerated (Whole document).

11. Schmitt does not teach using HBsAg produced by *Pichia pastoris*.

12. Alpar teaches intranasal formulations of TT/DT vaccines against tetanus and diphtherias. Alpar teaches a verity of adjuvants for TT and DT vaccines to enhance immunogenicity of TT and DT following nasal delivery (2.3-2.5, pp 190-196). All these results show that TT and DT can be used for nasal immunization along or with mucosal adjuvants. As compared with solutions of TT/DT in PBS, the adjuvants used in the studies can successfully facilitate an

intranasal vaccination of TT/DT (Figure 9-10 and pp.191-193).

13. Isaka (2001) teaches intranasal administration of HBsAg (1ug-5ug) along or with rCTB as adjuvant in a mice model. Isaka teaches that both HBsAg vaccine formulations are safe and immunogenic, and rCTB is an effective mucosal adjuvant to enhance the immunogenicity of HBsAg.

14. EP0864649 teaches recombinant HBsAg vaccine produced in *Pichia pastoris* (see Description). EP0864649 teaches that recombinant HBsAg form into particles of 22 nm, in *Pichia pastoris*, which confers superior immunogenic characteristics (p. 3). EP0864649 also teaches that HBsAg vaccine produced in *Pichia pastoris* is more immunogenic than commercially available HBsAg vaccine (from Smith & Kline) (Example 6).

15. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine HBsAg produced by *Pichia pastoris* with TT, DT with or without Hib for intranasal immunization, as taught by Schmitt, Alpar and Isaka. One skilled in the art would have been motivated to do so in order to receive the expected benefit of mucosal immunization of multivalent vaccines, eliciting protection against several diseases at the same time, as suggested and taught by Schmitt, Alpar and Isaka. There would have been a reasonable expectation of success, given the knowledge that multivalent vaccine formulations of HBsAg with TT, DT and Hib have been proven to be safe and effective in protecting infants from diseases, as taught by Schmitt, given the knowledge that HBsAg, or TT/DT are safe for intranasal administration, as taught by Alpar and Isaka, and also given the knowledge that HBsAg produced by *Pichia pastoris* is more immunogenic than some commercially available HBsAg vaccine, as taught by EP0864649. Thus, the idea of combining HBsAg produced in

Pichia pastoris, TT and DT for nasal administration flows logically from their having been individually taught in the prior art. The mucosal immunization of a combination of HBsAg with TT, DT and Hib for their additive effects and more cost-effect efficient renders the invention *prima facie* obvious.

Response to Applicant's argument:

16. Applicant argues that (1) the effect of HBsAg on other antigens is not an inherent property of HBsAg because not all HBsAg have an immunoenhancing effect. The examiner has not provided the necessary evidence that all HBsAg have an immunoenhancing effect.

17. In response, Applicant's argument is not relevant because it is based on newly amended claims. The original claims were generically directed to all HBsAg as a mucosal immunoenhancer (see original Claim 1). Thus, it was Applicant, not the examiner, who was claiming "all HBsAg have an immunoenhancing effect". Based on the newly amended claim 1, this argument is moot.

18. Applicant argues that (2) the specification of the instant application demonstrates the unexpected and surprising results obtained with the multivalent vaccine formulation of the invention. The examples and figures show the ability of nasally administered HBsAg from *Pichia pastoris* to enhance the immunogenicity of various antigens.

19. Applicant's argument is considered but found not persuasive. Since the HBsAg produced by *Pichia pastoris* as a vaccine and its immunogenicity has been disclosed and taught by EP0864649, and the multivalent vaccine formulation comprising HBsAg + DTaP+Hib + inactivated poliovirus has been taught by Schmitt, the instant claims does not distinguish the

multivalent vaccine formulation from identical prior art products.

Remarks

20. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

BP
Bo Peng, Ph.D.
April 26, 2007

Bruce Campell

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SUPERVISORY PATENT EXAMINER
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